

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015717 A2

- (51) International Patent Classification⁷: **A61K**
- (21) International Application Number: PCT/US02/27149
- (22) International Filing Date: 13 August 2002 (13.08.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/313,374 17 August 2001 (17.08.2001) US
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **HARTMAN, George, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **TUCKER, Thomas, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SISKO, John, T.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SMITH, Anthony, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LUMMA, William, C., Jr.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:— *without international search report and to be republished upon receipt of that report**For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 03/015717 A2

(54) Title: TYROSINE KINASE INHIBITORS

(57) Abstract: The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals.

TITLE OF THE INVENTION

TYROSINE KINASE INHIBITORS

BACKGROUND OF THE INVENTION

5 The present invention relates to compounds which inhibit, regulate
and/or modulate tyrosine kinase signal transduction, compositions which contain
these compounds, and methods of using them to treat tyrosine kinase-dependent
diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis,
age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the
10 like in mammals.

The following is provided as background information only and should
not be taken as an admission that any subject matter discussed or that any reference
mentioned is prior art to the instant invention

15 Tyrosine kinases are a class of enzymes that catalyze the transfer
of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein
substrates. They play critical roles in signal transduction for a number of cell
functions via substrate phosphorylation. Though the exact mechanism of signal
transduction is still unclear, tyrosine kinases have been shown to be important
contributing factors in cell proliferation, carcinogenesis and cell differentiation.

20 Tyrosine kinases can be categorized as receptor type or non-receptor
type. Receptor type tyrosine kinases have an extracellular, a transmembrane, and an
intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

25 The receptor-type tyrosine kinases are comprised of a large number
of transmembrane receptors with diverse biological activity. In fact, about twenty
different subfamilies of receptor-type tyrosine kinases have been identified. One
tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR,
HER2, HER3, and HER4. Ligands of this subfamily of receptors include epithelial
growth factor, TGF- α , amphiregulin, HB-EGF, betacellulin and heregulin. Another
subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which
30 includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF- α and β

receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For
5 a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6):334-339, 1994, which is hereby incorporated by reference.

The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying
10 receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen *Oncogene*, 8:2025-2031 (1993), which is hereby incorporated by reference.

15 Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signaling pathways leading to numerous pathogenic conditions, including cancer, psoriasis and hyperimmune responses.

Several receptor-type tyrosine kinases, and the growth factors that bind thereto, have been suggested to play a role in angiogenesis, although some may
20 promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995). One such receptor-type tyrosine kinase is fetal liver kinase 1 or FLK-1. The human analog of FLK-1 is the kinase insert domain-containing receptor KDR, which is also known as vascular endothelial cell growth factor receptor 2 or VEGFR-2, since it binds VEGF with high affinity. Finally, the murine version of this receptor has also
25 been called NYK (Oelrichs et al., *Oncogene* 8(1):11-15, 1993). VEGF and KDR are a ligand-receptor pair that play an important role in the proliferation of vascular endothelial cells, and the formation and sprouting of blood vessels, termed vasculogenesis and angiogenesis, respectively.

Angiogenesis is characterized by excessive activity of vascular endo-

thelial growth factor (VEGF). VEGF is actually comprised of a family of ligands (Klagsburn and D'Amore, *Cytokine & Growth Factor Reviews* 7:259-270, 1996). VEGF binds the high affinity membrane-spanning tyrosine kinase receptor KDR and the related fms-like tyrosine kinase-1, also known as Flt-1 or vascular endothelial cell growth factor receptor 1 (VEGFR-1). Cell culture and gene knockout experiments indicate that each receptor contributes to different aspects of angiogenesis. KDR mediates the mitogenic function of VEGF whereas Flt-1 appears to modulate non-mitogenic functions such as those associated with cellular adhesion. Inhibiting KDR thus modulates the level of mitogenic VEGF activity. In fact, tumor growth has been shown to be susceptible to the antiangiogenic effects of VEGF receptor antagonists. (Kim et al., *Nature* 362, pp. 841-844, 1993).

Solid tumors can therefore be treated by tyrosine kinase inhibitors since these tumors depend on angiogenesis for the formation of the blood vessels necessary to support their growth. These solid tumors include histiocytic lymphoma, cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung, including lung adenocarcinoma and small cell lung cancer. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-ras, erb-B) is observed. Such cancers include pancreatic and breast carcinoma. Accordingly, inhibitors of these tyrosine kinases are useful for the prevention and treatment of proliferative diseases dependent on these enzymes.

The angiogenic activity of VEGF is not limited to tumors. VEGF accounts for most of the angiogenic activity produced in or near the retina in diabetic retinopathy. This vascular growth in the retina leads to visual degeneration culminating in blindness. Ocular VEGF mRNA and protein are elevated by conditions such as retinal vein occlusion in primates and decreased pO₂ levels in mice that lead to neovascularization. Intraocular injections of anti-VEGF monoclonal antibodies or VEGF receptor immunofusions inhibit ocular neovascularization in both primate and rodent models. Regardless of the cause of induction of VEGF in human diabetic retinopathy, inhibition of ocular VEGF is useful in treating the disease.

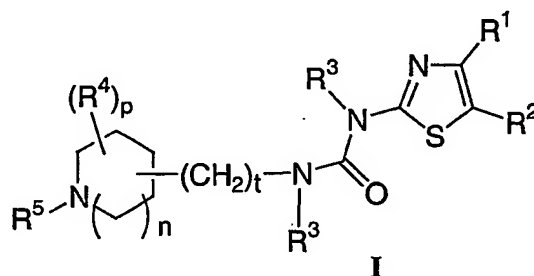
Expression of VEGF is also significantly increased in hypoxic regions of animal and human tumors adjacent to areas of necrosis. VEGF is also upregulated by the expression of the oncogenes ras, raf, src and mutant p53 (all of which are relevant to targeting cancer). Monoclonal anti-VEGF antibodies inhibit the growth of human tumors in nude mice. Although these same tumor cells continue to express VEGF in culture, the antibodies do not diminish their mitotic rate. Thus tumor-derived VEGF does not function as an autocrine mitogenic factor. Therefore, VEGF contributes to tumor growth in vivo by promoting angiogenesis through its paracrine vascular endothelial cell chemotactic and mitogenic activities. These monoclonal antibodies also inhibit the growth of typically less well vascularized human colon cancers in athymic mice and decrease the number of tumors arising from inoculated cells.

Viral expression of a VEGF-binding construct of Flk-1, Flt-1, the mouse KDR receptor homologue, truncated to eliminate the cytoplasmic tyrosine kinase domains but retaining a membrane anchor, virtually abolishes the growth of a transplantable glioblastoma in mice presumably by the dominant negative mechanism of heterodimer formation with membrane spanning endothelial cell VEGF receptors. Embryonic stem cells, which normally grow as solid tumors in nude mice, do not produce detectable tumors if both VEGF alleles are knocked out. Taken together, these data indicate the role of VEGF in the growth of solid tumors. Inhibition of KDR or Flt-1 is implicated in pathological angiogenesis, and these receptors are useful in the treatment of diseases in which angiogenesis is part of the overall pathology, e.g., inflammation, diabetic retinal vascularization, as well as various forms of cancer since tumor growth is known to be dependent on angiogenesis. (Weidner et al., N. Engl. J. Med., 324, pp. 1-8, 1991).

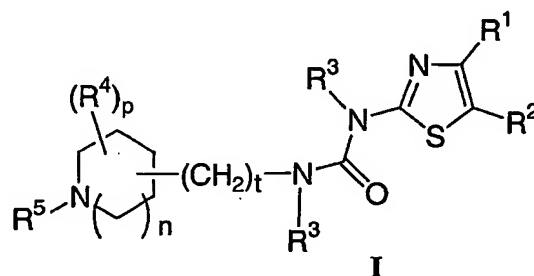
Accordingly, the identification of small compounds which specifically inhibit, regulate and/or modulate the signal transduction of tyrosine kinases is desirable and is an object of this invention.

SUMMARY OF THE INVENTION

The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts and stereoisomers thereof:

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

n is 0, 1, 2, or 3;

p is 0, 1, or 2;

t is 0, 1, or 2;

R¹ is H, halo or C₁₋₈ alkyl;

R² is phenyl, CN, (C=O)NR^aR^b, halo, C₃₋₆ cycloalkyl or -C≡C-R^c;

5 R³ is independently H, C₁₋₈ alkyl, SO₂R^d, (C=O)R^d, or CO₂R^d;

R⁴ is H, C₁₋₈ alkyl, halo, OH, or C₁₋₈ alkoxy;

R⁵ is H, C₁₋₈ alkyl, phenyl, SO₂R^d, (C=O)R^d, or CO₂R^d;

10

R^a and R^b are independently selected from H, C₁₋₆ alkyl, phenyl, CO₂R^d, (C=O)R^d, and SO₂R^d;

R^c is H, phenyl, or C₁₋₆ alkyl; and

15

R^d is phenyl, C₁₋₆ alkyl, or benzyl.

A second embodiment is the compound of Formula I described above, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R² is phenyl or CN.

20

A third embodiment is the compound of Formula I described above, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein n is 1 or 2.

Another embodiment is the compound of Formula I described above, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹, R³, and R⁴ are H; and R² is phenyl.

25

And yet a further embodiment is a compound selected from:

benzyl 4-[[[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl] amino)methyl]piperidine-1-carboxylate;
N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea;

N-(5-phenylthiazol-2-yl)-N'-(R,S)-3-aminopiperidin-3-yl)urea; and

4-[[{[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl} amino)methyl]piperidine;
or a pharmaceutically acceptable salt or stereoisomer thereof.

Also included within the scope of the present invention is a
5 pharmaceutical composition which is comprised of a compound of Formula I as
described above and a pharmaceutically acceptable carrier. The present invention
also encompasses a method of treating or preventing cancer in a mammal in need of
such treatment which is comprised of administering to said mammal a therapeutically
effective amount of a compound of Formula I. Preferred cancers for treatment are
10 selected from cancers of the brain, genitourinary tract, lymphatic system, stomach,
larynx and lung. Another set of preferred forms of cancer are histiocytic lymphoma,
lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and
breast carcinoma.

Also included is a method of treating or preventing a disease in which
15 angiogenesis is implicated, which is comprised of administering to a mammal in need
of such treatment a therapeutically effective amount of a compound of Formula I.
Such a disease in which angiogenesis is implicated is ocular diseases such as retinal
vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Also included within the scope of the present invention is a method
20 of treating or preventing inflammatory diseases which comprises administering to a
mammal in need of such treatment a therapeutically effective amount of a compound
of Formula I. Examples of such inflammatory diseases are rheumatoid arthritis,
psoriasis, contact dermatitis, delayed hypersensitivity reactions, and the like.

Also included is a method of treating or preventing a tyrosine kinase-
25 dependent disease or condition in a mammal which comprises administering to a
mammalian patient in need of such treatment a therapeutically effective amount of
a compound of Formula I. The therapeutic amount varies according to the specific
disease and is discernable to the skilled artisan without undue experimentation.

A method of treating or preventing retinal vascularization which is
30 comprised of administering to a mammal in need of such treatment a therapeutically

effective amount of compound of Formula I is also encompassed by the present invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention. Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

The invention also contemplates the use of the instantly claimed compounds in combination with a second compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 9) a reverse transcriptase inhibitor, and
- 10) another angiogenesis inhibitor.

Preferred angiogenesis inhibitors are selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamido-triazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of

Formula I in combination with radiation therapy and/or in combination with a compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 5 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 10 8) an HIV protease inhibitor,
- 9) a reverse transcriptase inhibitor, and
- 10) another angiogenesis inhibitor.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

Also within the scope of the invention is a method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of Formula I.

Another embodiment of the invention is a method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

These and other aspects of the invention will be apparent from the teachings contained herein.

"Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include the proliferation of tumor cells, the pathologic neovascularization that supports solid tumor growth, ocular neovascularization (diabetic retinopathy,

age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. These and other aspects of the invention will be apparent from the teachings contained herein.

Utilities

The instantly disclosed compounds are inhibitors of tyrosine kinase and are therefore useful to treat or prevent tyrosine kinase-dependent diseases or conditions in mammals.

“Tyrosine kinase-dependent diseases or conditions” refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include the proliferation of tumor cells, the pathologic neovascularization that supports solid tumor growth, ocular neovascularization (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like). In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

The present invention encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering

to said mammal a therapeutically effective amount of a compound of Formula I. Preferred cancers for treatment are selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. Another set of preferred forms of cancer are histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. *Cancer Research*, 55:4575-4580, 1995, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi et al., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); bladder carcinomas (A.J. Dickinson et al., *Br. J. Urol.*, 1994, 74:762-766); colon carcinomas (L.M. Ellis et al., *Surgery*, 1996, 120(5):871-878); and oral cavity tumors (J.K. Williams et al., *Am. J. Surg.*, 1994, 168:373-380).

Tumors which have undergone neovascularization show an increased potential for metastasis. VEGF released from cancer cells enhances metastasis possibly by increasing extravasation at points of adhesion to vascular endothelium. (A. Amirkhosravi et al., *Platelets*, 10:285-292 (1999)). In fact, angiogenesis is essential for tumor growth and metastasis. (S.P. Gunningham, et al., *Can. Research*, 61: 3206-3211 (2001)). The angiogenesis inhibitors disclosed in the present application are therefore also useful to prevent or decrease tumor cell metastasis. Such a use is also contemplated to be within the scope of the present invention.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 June 2000). The undesirable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood

vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

5 Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I. Examples of such inflammatory diseases are rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions, and the like.
10 (A. Giatromanolaki et al., *J. Pathol.* 2001; 194:101-108). For the role of VEGF in skin angiogenesis, see Michael Detmar, *J. Dermatological Sci.*, 24 Suppl. 1, S78-S84 (2000).

 Also included within the scope of the present invention is a method of treating or preventing bone associated pathologies selected from osteosarcoma,
15 osteoarthritis, and rickets, also known as oncogenic osteomalacia. (Hasegawa et al., *Skeletal Radiol.*, 28, pp.41-45, 1999; Gerber et al., *Nature Medicine*, Vol. 5, No. 6, pp.623-628, June 1999). And since VEGF directly promotes osteoclastic bone resorption through KDR/Flk-1 expressed in mature osteoclasts (*FEBS Let.* 473:161-164 (2000); *Endocrinology*, 141:1667 (2000)), the instant compounds are also useful
20 to treat and prevent conditions related to bone resorption, such as osteoporosis and Paget's disease.

 A method of treating or preventing preeclampsia is also within the which comprises administering a therapeutically effective amount of a compound of Formula I. Studies have shown that the action of VEGF on the Flt-1 receptor is
25 pivotal in the pathogenesis of preeclampsia. (*Laboratory Investigation* 79:1101-1111 (September 1999)). Vessels of pregnant women incubated with VEGF exhibit a reduction in endothelium-dependent relaxation similar to that induced by plasma from women with preeclampsia. In the presence of an anti-Flt-1 receptor antibody, however, neither VEGF or plasma from women with preeclampsia reduced the

endothelium-dependent relaxation. Therefore the claimed compounds serve to treat preeclampsia via their action on the tyrosine kinase domain of the Flt-1 receptor.

Also within the scope of the invention is a method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of Formula I. The claimed compounds can also be used to reduce or prevent tissue damage which occurs after cerebral ischemic events, such as stroke, by reducing cerebral edema, tissue damage, and reperfusion injury following ischemia. (*Drug News Perspect* 11:265-270 (1998); *J. Clin. Invest.* 104:1613-1620 (1999); *Nature Med* 7:222-227 (2001)).

The instant compounds can also be used to prevent or treat tissue damage during bacterial meningitis, such as tuberculous meningitis. Matsuyama et al., *J. Neurol. Sci.* 186:75-79 (2001)). The instant invention therefore encompasses a method of treating or preventing tissue damage due to bacterial meningitis which comprises administering a therapeutically effective amount of a compound of Formula 1. Studies have shown that VEGF is secreted by inflammatory cells during bacterial meningitis and that VEGF contributes to blood-brain barrier disruption. (van der Flier et al., *J. Infectious Diseases*, 183:149-153 (2001)). The claimed compounds can inhibit VEGF-induced vascular permeability and therefore serve to prevent or treat blood-brain barrier disruption associated with bacterial meningitis.

The present invention further encompasses a method to treat or prevent endometrioses comprised of administering a therapeutically effective amount of a compound of Formula I. An increase in VEGF expression and angiogenesis is associated with the progression of endometriosis (Stephen K. Smith, *Trends in Endocrinology & Metabolism*, Vol. 12, No. 4, May/June 2001). Inhibition of VEGF by the current compounds would therefore inhibit angiogenesis and treat endometriosis.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a

pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

5 For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral
10 administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared,
15 and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen
20 receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadministered with radiation therapy. The synergistic effects of inhibiting
25 VEGF in combination with radiation therapy have been described in the art (see WO 00/61186).

"Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene,
30 idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-

oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

“Androgen receptor modulators” refers to compounds which
 5 interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds which interfere
 or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples
 10 of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

“Cytotoxic agents” refer to compounds which cause cell death
 primarily by interfering directly with the cell's functioning or inhibit or interfere
 15 with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to,
 tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin,
 altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin,
 20 oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methylpyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum
 25 (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-
 30 methylsulphonyl-daunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed,

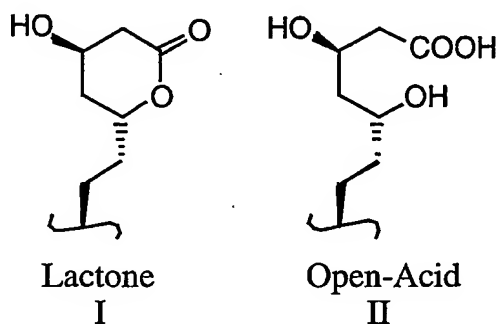
pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent No. 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and

BAYCHOL[®]; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314.

- 5 The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the
10 lactone portion and its corresponding open-acid form is shown below as structures I and II.



- 15 In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically
20 acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from

amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further

5 examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide,

10 hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

15 Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which

20 inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-

25 yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-

(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)
methyl]-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-
5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-
2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-
5 cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-
4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}
benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-
methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-
3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-
10 5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']
bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-
1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-
19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxazacyclo-
nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-
15 6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-
carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-
22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-
dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo
[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

20 Other examples of prenyl-protein transferase inhibitors can be
found in the following publications and patents: WO 96/30343, WO 97/18813,
WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119,
WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent
No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent
25 No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112,
European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357,
WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S.
Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535,
WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443,
30 WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612,

- WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792,
 WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017,
 WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477,
 WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050,
 5. WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246,
 WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359.

For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

- Examples of HIV protease inhibitors include amprenavir, abacavir,
 10 CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir,
 saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse
 transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097,
 lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

- “Angiogenesis inhibitors” refers to compounds that inhibit the
 15 formation of new blood vessels, regardless of mechanism. Examples of angiogenesis
 inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors
 of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20),
 inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors,
 MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- α , interleukin-
 20 12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-
 inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-
 genase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992);
 JNCI, Vol. 69, p. 475 (1982); Arch. Ophthalmol., Vol. 108, p.573 (1990); Anat. Rec.,
 Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin. Orthop. Vol. 313,
 25 p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75,
 p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998);
 Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)),
 carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-
 fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see
 30 Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF

(see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim et al., Nature, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC₅₀ for the inhibition of COX-2 of 1 μ M or less as measured by cell or microsomal assay..

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by cell or microsomal assay. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, issued December 12, 1995, U.S. Patent 5,861,419, issued January 19, 1999, U.S. Patent 6,001,843, issued December 14, 1999, U.S. Patent 6,020,343, issued February 1, 2000, U.S. Patent 5,409,944, issued April 25, 1995, U.S. Patent 5,436,265, issued July 25, 1995, U.S. Patent 5,536,752, issued July 16, 1996, U.S. Patent 5,550,142, issued August 27, 1996, U.S. Patent 5,604,260, issued February 18, 1997, U.S. Patent 5,698,584, issued December 16, 1997, U.S. Patent 5,710,140, issued January 20, 1998, WO 94/15932, published July 21, 1994, U.S. Patent 5,344,991, issued June 6, 1994, U.S. Patent 5,134,142, issued July 28, 1992, U.S. Patent 5,380,738, issued January 10, 1995, U.S. Patent 5,393,790, issued February 20, 1995, U.S. Patent 5,466,823, issued November 14, 1995, U.S. Patent 5,633,272, issued May 27, 1997, and U.S. Patent 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Other examples of specific inhibitors of COX-2 include the following:

- 3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
- 3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
- 3-(3,4-dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
- 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
- 5,5-dimethyl-3-(3-fluorophenyl)-4-(methylsulfonyl)phenyl)-2-(5H)-furanone;

- 3-(4-methylsulfonyl)phenyl-2-phenyl-5-trifluoromethylpyridine;
2-(3-chlorophenyl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethyl-pyridine;
2-(4-chlorophenyl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethyl-pyridine;
2-(4-fluorophenyl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethyl-pyridine;
5 3-(4-methylsulfonyl)phenyl-2-(3-pyridinyl)-5-trifluoromethylpyridine;
5-methyl-3-(4-methylsulfonyl)phenyl-2-phenylpyridine;
2-(4-chlorophenyl)-5-methyl-3-(4-methylsulfonyl) phenylpyridine;
5-methyl-3-(4-methylsulfonyl)phenyl-2-(3-pyridinyl) pyridine;
5-chloro-2-(4-chlorophenyl)-3-(4-methylsulfonyl) phenylpyridine;
10 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-pyridinyl) pyridine;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(3-pyridinyl) pyridine;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(4-pyridinyl) pyridine;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;
2-(4-chlorophenyl)-3-(4-methylsulfonyl)phenylpyridinyl-5-carboxylic acid methyl
15 ester;
2-(4-chlorophenyl)-3-(4-methylsulfonyl)phenylpyridinyl-5-carboxylic acid;
5-cyano-2-(4-chlorophenyl)-3-(4-methylsulfonyl) phenylpyridine;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(3-pyridyl)pyridine hydromethanesulfonate;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(3-pyridyl)pyridine hydrochloride;
20 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine hydrochloride;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-ethyl-5-pyridinyl)pyridine;
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-ethyl-5-pyridinyl)pyridine
hydromethanesulfonate;
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
25 3-(3-fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(3,5-difluorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one;
3-phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(2,4-difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(4-chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
30 3-(3,4-dichlorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one;

- 3-(4-fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
3-(4-fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(3,5-difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
5 3-phenylthio-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
3-(N-methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
10 3-phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(3,4-difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(3,4-difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
15 3-benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
4-(4-(methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4.4]non-3-en-2-one;
4-(4-(methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one;
4-(2-oxo-3-phenylthio-1-oxa-spiro[4.4]non-3-en-4-yl) benzenesulfonamide;
3-(4-fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
20 3-(3,4-difluorophenoxy)-5-methoxy-5-methyl-4-(4- (methylsulfonyl)phenyl)-5H-furan-2-one;
3-(5-chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
25 3-(6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
3-(3-isoquinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(4-(methylsulfonyl)phenyl)-2-phenoxy-cyclopent-2-enone;
3-(4-(methylsulfonyl)phenyl)-2-(3,4-difluorophenoxy)cyclopent-2-enone;

- 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(5-bromopyridin-2-yloxy)-5H-furan-2-one;
- 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one;
- 2-(3,4-difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone;
- 5 3-(5-benzothiophenyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
- 5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridyl-4-oxy)-5H-furan-2-one;
- 5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridyl-3-oxy)-5H-furan-2-one;
- 3-(2-methyl-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-
- 10 one;
- 3-(2-fluoro-4-trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;
- 3-(5-chloro-2-pyridylthio)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 2-(3,5-difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone;
- 15 3-(2-pyrimidinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(3-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(3-chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
- 3-(3-(1,2,5-thiadiazolyl)oxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-
- 20 one;
- 3-(5-isoquinolinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(6-amino-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
- 3-(3-chloro-4-fluoro)phenoxy-4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-
- 25 one;
- 3-(6-quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 3-(5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(2-thiazolylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 3-(3-chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-
- 30 one;

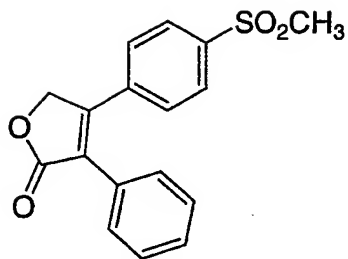
- 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one;
3-(3-trifluoromethyl)phenoxy-4-(4-methylsulfonylphenyl)-5,5-dimethyl-5H-furan-2-one;
5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(piperidine-1-carbonyl)-5-H-furan-2-one;
5 5,5-dimethyl-3-(2-Butoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentoxy)-5H-furan-2-one;
2-(5-chloro-2-pyridyloxy)-3-(4-methylsulfonyl)phenylcyclopent-2-enone;
3-(4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
10 (5R)-3-(3,4-difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
(5R)-3-(4-chlorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
3-(2-methyl-3-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
15 3-(4-methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
3-(5-chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
3-(5-fluoro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
20 3-(3-chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
3-(4-fluorophenoxy)-5-methyl-4-(4-methylsulfonylphenyl)-5-propyl-5H-furan-2-one;
3-(N,N-diethylamino)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(3,5-dichloro-2-pyridyloxy)-5H-furan-2-one;
25 one;
(5R)-3-(4-bromophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;
(5R)-3-(4-methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one;

- (5R)-3-(5-chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one;
- 3-(5-chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one;
- 5 3-(1-cyclopropyl-ethoxy)-5,5-dimethyl-4-(4-methyl sulfonyl)phenyl)-5H-furan-2-one;
- 5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-(propoxy)-5-(2-trifluoroethyl)-5H-furan-2-one;
- 5(R)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
- 5,5-dimethyl-3-(2,2-dimethylpropyloxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-
- 10 one;
- 5(R)-3-(1-cyclopropyl-ethoxy)-5-ethyl-5-methyl-4-(4-(methyl sulfonyl)phenyl)-5H-furan-2-one;
- 5(S)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
- 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 15 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 5,5-dimethyl-3-(isobutoxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 3-(4-bromophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 3-(2-quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 3-(2-chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-
- 20 one;
- 3-(6-benzothiazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
- 3-(6-chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one;
- 3-(4-quinazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 25 (5R)-3-(5-fluoro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-(4-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-(5-fluoro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-
- 30 trifluoroethyl)-5H-furan-2-one;

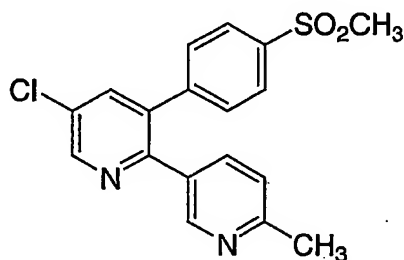
- 3-(1-isoquinolinyloxy)-5,5-dimethyl-4-(methylsulfonyl)phenyl-5H-furan-2-one;
(5R)-3-(4-fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one;
- 3-(3-fluoro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 5 (5R)-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one;
- (5R)-3-(5-chloro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 10 3-(3,4-difluorophenoxy)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propyl-5H-furan-2-one;
- 3-cyclobutyloxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(1-indanyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
- 15 3-(2-indanyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-cyclopentyloxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(3,3-dimethylcyclopentyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-isopropoxy-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one;
- 20 3-(2-methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 3-(5-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5RS)-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one;
- 25 3-(3-chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-(3-chloro-4-methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-(4-chlorophenoxy)-5-trifluoroethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 30

- (5R)-3-(4-bromophenoxy)-5-trifluoroethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
5-cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 5 (5R)-3-(3-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
(5R)-3-(4-chloro-3-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-phenoxy-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 10 (5R)-3-(4-chloro-3-methylphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
3-(4-chloro-3-methylphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- (5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one;
- 15 (5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-ethyl-5-methyl-5H-furan-2-one;
3-(5-chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
- 20 3-(5-cyclopropyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
3-(1-cyclopropylethoxy)-4-(4-methylsulfonyl)phenyl-5H-furan-2-one; and
3-(cyclopropylmethoxy)-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;
or a pharmaceutically acceptable salt or stereoisomer thereof.
- 25 Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and



5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;



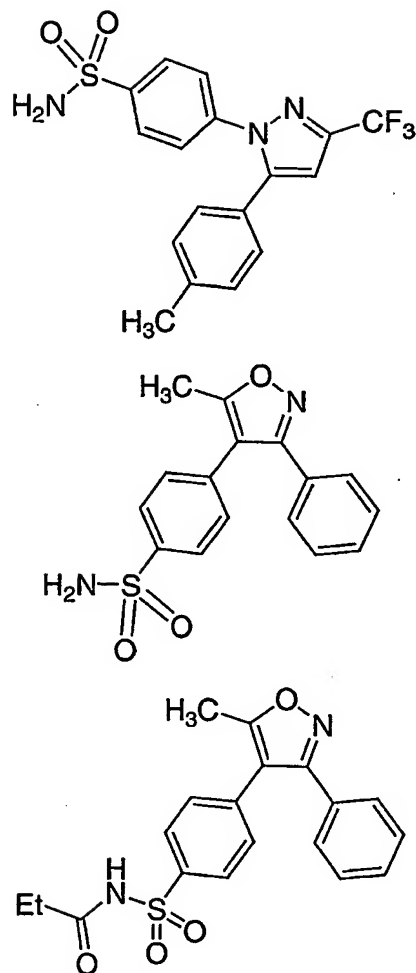
5

or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:

15



5 or a pharmaceutically acceptable salt thereof.

Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

10

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, U.S. Patent No. 6,001,843, issued December 14, 1999, U.S. Patent No. 6,020,343, issued February 1, 2000, U.S. Patent No. 5,409,944, issued April 25, 1995, U.S. Patent No. 5,436,265, issued July 25, 1995, U.S. Patent No. 5,536,752, issued July 16, 1996, U.S. Patent No. 5,550,142, issued August 27, 1996, U.S. Patent No. 5,604,260, issued February 18, 1997, U.S. Patent No. 5,698,584, issued December 16, 1997, and U.S. Patent No. 5,710,140, issued January 20, 1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, tiazosin, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, 5 N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo [2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7- 10 dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit 15 metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with 20 GP IIb/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrافiban, lamifiban, lotrafiban, cromofiban, and CT50352.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of 25 the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of 30 treatment. When a compound of the invention or prodrug thereof is provided in

combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg

of body weight per day.

The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second compound selected from:

- 1) an estrogen receptor modulator,
- 5 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 10 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 9) a reverse transcriptase inhibitor, and
- 10) another angiogenesis inhibitor.

Preferred angiogenesis inhibitors to be used as the second compound
15 are a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamido-triazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillool,
20 thalidomide, angiostatin, troponin-1, or an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a
25 compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 30 5) an antiproliferative agent,

- 6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
5 10) another angiogenesis inhibitor.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formual I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing
10 cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

These and other aspects of the invention will be apparent from the teachings contained herein.

15 Definitions

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereo-chemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers,
20 with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms, and mixtures thereof, are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

25 When any variable occurs more than one time in any constituent, such as R³, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the
30 substitutable ring atoms. If the ring system is polycyclic, it is intended that the

bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized
5 by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

As used herein, "alkyl" is intended to include both branched and unbranched, cyclic and acyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₁₀, as in "C₁-C₁₀ alkyl" is
10 defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement and may be cyclic or acyclic. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In some instances, definitions
15 may appear for the same variable reciting both alkyl and cycloalkyl when a different number of carbons is intended for the respective substituents. The use of both terms in one definition should not be interpreted to mean in another definition that "alkyl" does not encompass "cycloalkyl" when only "alkyl" is used. "Cycloalkyl", however, does not encompass non-cyclic alkyls.

20 "Alkoxy" represents an alkyl group of indicated number of carbon atoms as defined above attached through an oxygen bridge. The term "C₁-6 alkoxy" is therefore equivalent to "OC₁₋₆ alkyl".

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

25 The alkyl, cycloalkyl, and phenyl substituents may be substituted or unsubstituted, unless specifically defined otherwise. For example, a (C₁-C₆)alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, and dialkylamino. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: -(C=O)CH₂CH(OH)CH₃,
30 -(C=O)OH, -CH₂(OH)CH₂CH(O), and so on.

The pharmaceutically acceptable salts encompassed by the present invention can be synthesized from the disclosed compounds which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by
5 reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic,
10 propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. Similarly, the salts of the acidic compounds are formed by reactions with conventional inorganic or organic bases.

15 Preferably R^1 is H. Preferably R^2 is CN or phenyl. Most preferably R^2 is phenyl. R^3 is preferably H. n is preferably 0 or 1. Most preferably n is 1. t is preferably 0 or 1.

The compounds of this invention may be prepared by employing reactions as shown in the following scheme, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures.
20 This scheme, therefore, is not limited by the compounds shown or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the scheme does not necessarily correlate to that used in the claims.

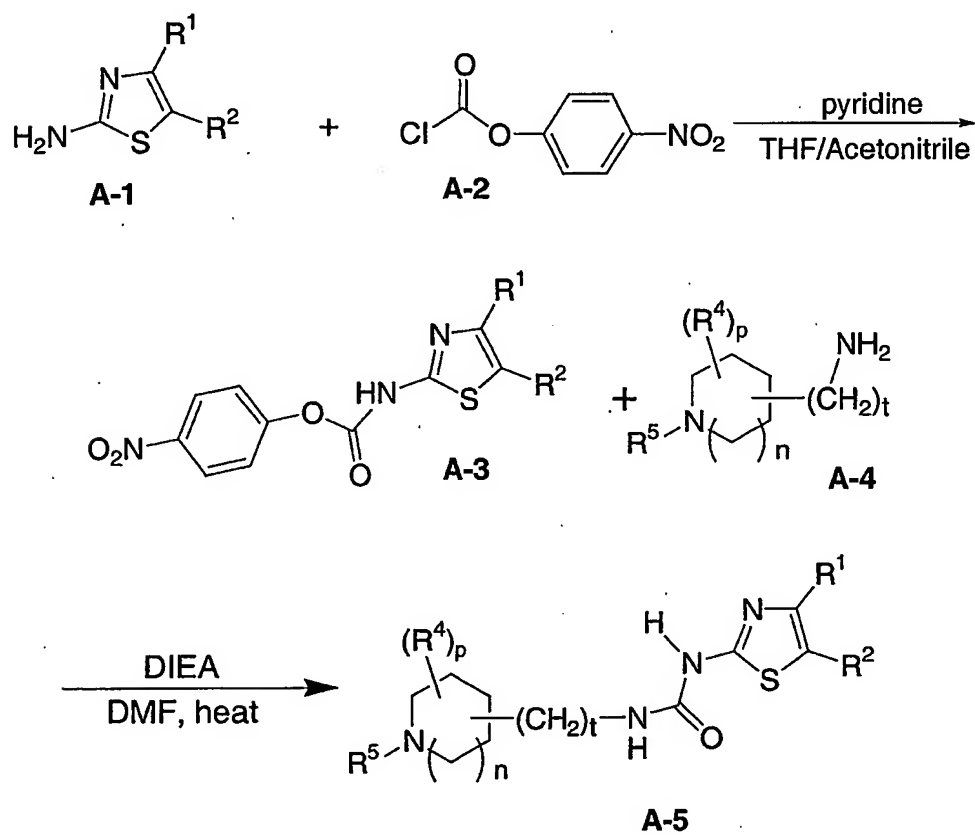
25

SCHEMES

Synopsis of Schemes

As shown in Scheme A, the compounds of the instant invention may be synthesized by activating the amino thiazole A-1 with p-nitrophenyl-chloroformate A-2, followed by coupling with the appropriate amine A-4.

5

SCHEME A

ASSAYS

The compounds of the instant invention described in the Examples were tested by the assays described below and were found to have kinase inhibitory activity. Other assays are known in the literature and could be readily performed by those of skill in the art (see, for example, Dhanabal et al., *Cancer Res.* 59:189-197; Xin et al., *J. Biol. Chem.* 274:9116-9121; Sheu et al., *Anticancer Res.* 18:4435-4441; Ausprunk et al., *Dev. Biol.* 38:237-248; Gimbrone et al., *J. Natl. Cancer Inst.* 52:413-427; Nicosia et al., *In Vitro* 18:538-549).

10

I. VEGF RECEPTOR KINASE ASSAY

VEGF receptor kinase activity is measured by incorporation of radio-labeled phosphate into polyglutamic acid, tyrosine, 4:1 (pEY) substrate. The phosphorylated pEY product is trapped onto a filter membrane and the incorporation of radio-labeled phosphate quantified by scintillation counting.

15

MATERIALS

VEGF Receptor Kinase

The intracellular tyrosine kinase domains of human KDR (Terman, B.I. et al. *Oncogene* (1991) vol. 6, pp. 1677-1683.) and Flt-1 (Shibuya, M. et al. *Oncogene* (1990) vol. 5, pp. 519-524) were cloned as glutathione S-transferase (GST) gene fusion proteins. This was accomplished by cloning the cytoplasmic domain of the KDR kinase as an in frame fusion at the carboxy terminus of the GST gene. Soluble recombinant GST-kinase domain fusion proteins were expressed in *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

20

25

The other materials used and their compositions were as follows:

30

Lysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.5% triton X-100, 10% glycerol, 10 µg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethanesulfonyl fluoride (all Sigma).

- 5 Wash buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 10% glycerol, 10 µg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethanesulfonyl fluoride.

- 10 Dialysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 50% glycerol, 10 µg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethanesulfonyl fluoride.

10 X reaction buffer: 200 mM Tris, pH 7.4, 1.0 M NaCl, 50 mM MnCl₂, 10 mM DTT and 5 mg/mL bovine serum albumin (Sigma).

15

Enzyme dilution buffer: 50 mM Tris, pH 7.4, 0.1 M NaCl, 1 mM DTT, 10% glycerol, 100 mg/mL BSA.

10 X Substrate: 750 µg/mL poly (glutamic acid, tyrosine; 4:1) (Sigma).

20

Stop solution: 30% trichloroacetic acid, 0.2 M sodium pyrophosphate (both Fisher).

Wash solution: 15% trichloroacetic acid, 0.2 M sodium pyrophosphate.

- 25 Filter plates: Millipore #MAFC NOB, GF/C glass fiber 96 well plate.

METHOD

A. Protein purification

1. Sf21 cells were infected with recombinant virus at a
5 multiplicity of infection of 5 virus particles/ cell and grown at 27°C for 48 hours.
2. All steps were performed at 4°C. Infected cells were harvested
by centrifugation at 1000 X g and lysed at 4°C for 30 minutes with 1/10 volume of
lysis buffer followed by centrifugation at 100,000Xg for 1 hour. The supernatant was
then passed over a glutathione Sepharose column (Pharmacia) equilibrated in lysis
10 buffer and washed with 5 volumes of the same buffer followed by 5 volumes of wash
buffer. Recombinant GST-KDR protein was eluted with wash buffer/10 mM reduced
glutathione (Sigma) and dialyzed against dialysis buffer.

B. VEGF receptor kinase assay

- 15 1. Add 5 µl of inhibitor or control to the assay in 50% DMSO.
2. Add 35 µl of reaction mix containing 5 µl of 10 X reaction buffer;
5 µl 25 mM ATP/10 µCi [³³P]ATP (Amersham), and 5 µl 10 X substrate.
3. Start the reaction by the addition of 10 µl of KDR (25 nM) in
enzyme dilution buffer.
- 20 4. Mix and incubate at room temperature for 15 minutes.
5. Stop by the addition of 50 µl stop solution.
6. Incubate for 15 minutes at 4°C.
7. Transfer a 90µl aliquot to filter plate.
8. Aspirate and wash 3 times with wash solution.
- 25 9. Add 30 µl of scintillation cocktail, seal plate and count in a Wallac
Microbeta scintillation counter.

II. HUMAN UMBILICAL VEIN ENDOTHELIAL CELL MITOGENESIS ASSAY

- Human umbilical vein endothelial cells (HUVECs) in culture
30 proliferate in response to VEGF treatment and can be used as an assay system to

quantify the effects of KDR kinase inhibitors on VEGF stimulation. In the assay described, quiescent HUVEC monolayers are treated with vehicle or test compound 2 hours prior to addition of VEGF or basic fibroblast growth factor (bFGF). The mitogenic response to VEGF or bFGF is determined by measuring the incorporation of [³H]thymidine into cellular DNA.

MATERIALS

HUVECs: HUVECs frozen as primary culture isolates are obtained from Clonetics Corp. Cells are maintained in Endothelial Growth Medium (EGM; Clonetics) and are used for mitogenic assays described in passages 3-7 below.

Culture Plates: NUNCCLON 96-well polystyrene tissue culture plates (NUNC #167008).

Assay Medium: Dulbecco's modification of Eagle's medium containing 1 g/mL glucose (low-glucose DMEM; Mediatech) plus 10% (v/v) fetal bovine serum (Clonetics).

Test Compounds: Working stocks of test compounds are diluted serially in 100% dimethylsulfoxide (DMSO) to 400-fold greater than their desired final concentrations. Final dilutions to 1X concentration are made directly into Assay Medium immediately prior to addition to cells.

10X Growth Factors: Solutions of human VEGF₁₆₅ (500 ng/mL; R&D Systems) and bFGF (10 ng/mL; R&D Systems) are prepared in Assay Medium.

10X [³H]Thymidine: [Methyl-³H]thymidine (20 Ci/mmol; Dupont-NEN) is diluted to 80 µCi/mL in low-glucose DMEM.

Cell Wash Medium: Hank's balanced salt solution (Mediatech) containing 1 mg/mL bovine serum albumin (Boehringer-Mannheim).

Cell Lysis Solution: 1 N NaOH, 2% (w/v) Na₂CO₃.

5

METHOD

1. HUVEC monolayers maintained in EGM are harvested by trypsinization and plated at a density of 4000 cells per 100 μ L Assay Medium per well
10 in 96-well plates. Cells are growth-arrested for 24 hours at 37°C in a humidified atmosphere containing 5% CO₂.

2. Growth-arrest medium is replaced by 100 μ L Assay Medium containing either vehicle (0.25% [v/v] DMSO) or the desired final concentration of test compound. All determinations are performed in triplicate. Cells are then
15 incubated at 37°C with 5% CO₂ for 2 hours to allow test compounds to enter cells.

3. After the 2-hour pretreatment period, cells are stimulated by addition of 10 μ L/well of either Assay Medium, 10X VEGF solution or 10X bFGF solution. Cells are then incubated at 37°C and 5% CO₂.

4. After 24 hours in the presence of growth factors, 10X [³H]
20 thymidine (10 μ L/well) is added.

5. Three days after addition of [³H]thymidine, medium is removed by aspiration, and cells are washed twice with Cell Wash Medium (400 μ L/well followed by 200 μ L/well). The washed, adherent cells are then solubilized by addition of Cell Lysis Solution (100 μ L/well) and warming to 37°C for 30 minutes. Cell lysates are
25 transferred to 7-mL glass scintillation vials containing 150 μ L of water. Scintillation cocktail (5 mL/vial) is added, and cell-associated radioactivity is determined by liquid scintillation spectroscopy.

Based upon the foregoing assays the compounds of Formula I are inhibitors of VEGF and thus are useful for the inhibition of angiogenesis, such as
30 in the treatment of ocular disease, e.g., diabetic retinopathy and in the treatment

of cancers, e.g., solid tumors. The instant compounds inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC₅₀ values between 0.01 - 5.0 μ M. These compounds may also show selectivity over related tyrosine kinases (e.g., FGFR1 and the Src family; for relationship between Src kinases and VEGFR kinases, see Eliceiri et al., Molecular Cell, Vol. 4, pp.915-924, December 1999).

III. FLT-1 KINASE ASSAY

Flt-1 was expressed as a GST fusion to the Flt-1 kinase domain and was expressed in baculovirus/insect cells. The following protocol was employed to assay compounds for Flt-1 kinase inhibitory activity:

1. Inhibitors were diluted to account for the final dilution in the assay, 1:20.
2. The appropriate amount of reaction mix was prepared at room temperature:
 - 10X Buffer (20 mM Tris pH 7.4/0.1 M NaCl/1mM DTT final)
 - 0.1M MnCl₂ (5mM final)
 - pEY substrate (75 μ g/mL)
 - ATP/[³³P]ATP (2.5 μ M/1 μ Ci final)
 - BSA (500 μ g/mL final).
3. 5 μ L of the diluted inhibitor was added to the reaction mix. (Final volume of 5 μ L in 50% DMSO). To the positive control wells, blank DMSO (50%) was added.
4. 35 μ L of the reaction mix was added to each well of a 96 well plate.
5. Enzyme was diluted into enzyme dilution buffer (kept at 4°C).
6. 10 μ L of the diluted enzyme was added to each well and mix (5 nM final). To the negative control wells, 10 μ L 0.5 M EDTA was added per well instead (final 100 mM).
7. Incubation was then carried out at room temperature for 30 minutes.
8. Stopped by the addition of an equal volume (50 μ L) of 30% TCA/0.1M Na pyrophosphate.

9. Incubation was then carried out for 15 minutes to allow precipitation.
10. Transferred to Millipore filter plate.
11. Washed 3X with 15% TCA/0.1M Na pyrophosphate (125 μ L per wash).
12. Allowed to dry under vacuum for 2-3 minutes.
- 5 13. Dried in hood for ~ 20 minutes.
14. Assembled Wallac Millipore adapter and added 50 μ L of scintillant to each well and counted.

EXAMPLES

10

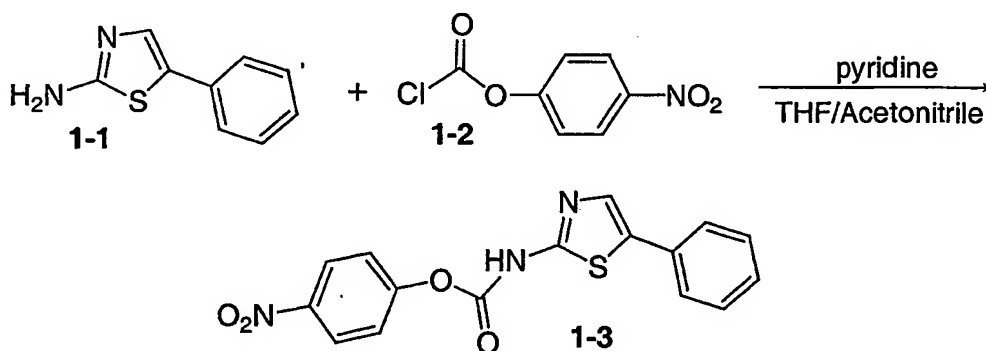
Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

15

EXAMPLE 1

20

Scheme 1: Synthesis of 2-(4-nitrophenoxy)carbonylamino-5-phenylthiazole (1-3)



To a solution of 1.36 g (7.72 mmol) of 2-aminothiazole 1-1 in 24 mL of 7:1 THF/acetonitrile was added 1.56 g (7.72 mmol) of p-nitrophenylchloroformate,

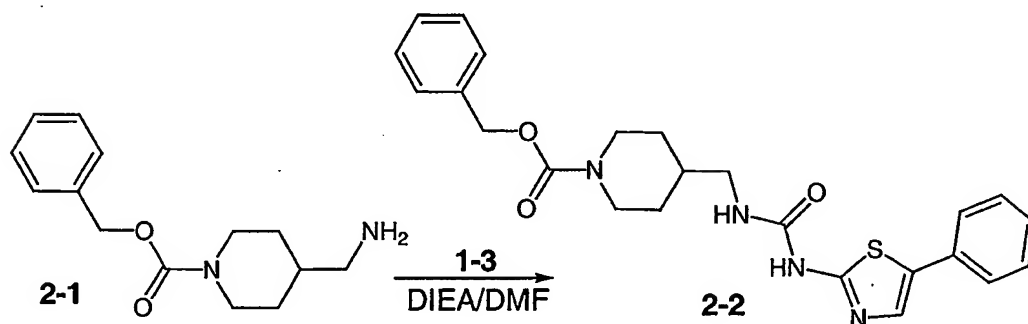
1-2, followed by 781 μ l (9.65 mmol) of pyridine. A thick yellow precipitate formed immediately. The resulting suspension was stirred vigorously at room temperature for 18 hours and then filtered. The yellow solid precipitate was washed several times with THF and dried in vacuo to provide 1-3.

5

EXAMPLE 2

Scheme 2: Synthesis of Benzyl 4-[[[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl]amino)methyl]piperidine-1-carboxylate (2-2)

10

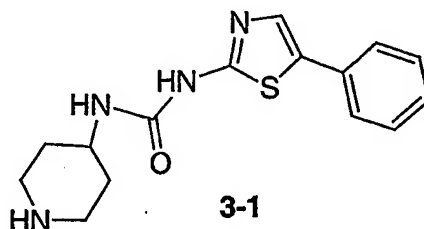


2-(4-nitrophenoxycarbonyl)amino-5-phenylthiazole 1-3 (0.59 mmol)
 15 along with benzyl 4-(aminomethyl)piperidine-1-carboxylate 2-1 (0.64mmol), diisopropylethylamine (2.1mmol), and dimethylformamide (2.0ml) were combined and heated at 60°C overnight. The reaction was poured into brine (25ml) containing ammoniumhydroxide (2.0ml). The mixture was extracted with ethylacetate (4x25ml) and the ethylacetate layer back extracted with additional brine/ammonium-
 20 hydroxide until the yellow color had faded. The ethylacetate layer was dried (MgSO₄), and the solvent removed to give 2-2. ¹H-NMR (500 MHz, CDCl₃):7.52 (3H, m), 7.35(7H, m,), 7.25(1H, m,), 5.53(1H, br m), 5.09(2H, s), 4.26(2H, d), 3.10(2H, m), 2.87(2H, t), 1.77(3H, m), 1.23(2H, m). High res. ES MS: Theoretical Mass 451.1809, Measured Mass 451.1798 (C₂₄H₂₆N₄O₃S+H⁺)

EXAMPLE 3

N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea (3-1)

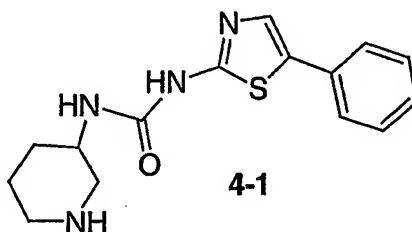
5



In a manner identical to that described above in Scheme 2, from 242 mg (0.71 mmol) of 2-(4-nitrophenoxy carbonyl)amino-5-phenylthiazole **1-3** and 220 mg (0.71 mmol) of the TFA salt of 1-trifluoroacetyl-4-aminopiperidine was obtained the crude trifluoroacetylated product. The product was dissolved in 3 mL methanol/2 mL DME/5 mL saturated aqueous K₂CO₃, and was stirred at 50°C for 18 hours. The reaction was cooled and was concentrated *in vacuo* to remove organics. The suspension was extracted twice with ethyl acetate, and the combined extracts dried and concentrated *in vacuo* to give an oily solid. The crude product was purified by reversed phase preparatory LC to give the TFA salt of **3-1** as a fluffy white amorphous solid. ¹H NMR(DMSO-d₆) : 1.60(dq,2H), 2.01(dd,2H), 3.30(m,2H), 3.27(dd,2H), 3.80(m,1H), 6.98(d,1H), 7.27(t,1H), 7.39(t,2H), 7.56(d,2H), 7.73(s,1H), 8.32 br s, 1H), 8.57(br s, 1H). High Res. FAB MS : Theo. Mass = 303.1274; measured mass = 303.1271.

EXAMPLE 4

N-(5-phenylthiazol-2-yl)-N' - ((R,S)-3-aminopiperidin-3-yl)urea (4-1)



In a manner identical to that described above in Scheme 2, from 200 mg (0.59 mmol) of 2-(4-nitrophenoxy carbonyl)amino-5-phenylthiazole **1-3** and 118 mg (0.59 mmol) of 1-Boc-3-(R,S)-aminopiperazine was obtained the crude Boc protected product. The product was dissolved in 1mL TFA/1mL methylene chloride, and was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo* to give crude desired product as an oil. The oil was purified by reversed phase preparatory LC to give the TFA salt of **4-1** as a fluffy white amorphous solid .

10

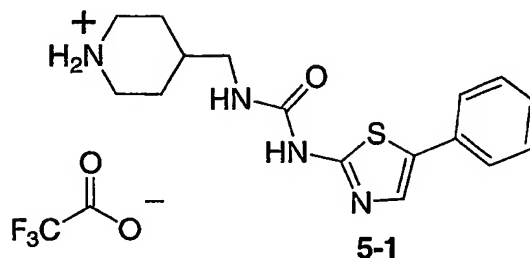
^1H NMR(DMSO- d_6) : 1.53(dq, 1H), 1.69(dq, 1H), 1.90(ddd, 1H), 2.85(m, 2H), 3.19(d, 1H), 3.33(d, 1H), 3.88(m, 1H), 6.92(d, 1H), 7.28(t, 1H), 7.40(t, 2H), 7.56(d, 2H), 7.74(s, 1H), 8.63(br, 1H), 8.75(br, 1H), 10.64(br s, 1H). High Res. FAB MS : Theo. Mass = 303.1274; measured mass = 303.1268.

15

EXAMPLE 5

4-([[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl] amino)methyl]piperidinium
trifluoroacetate (**5-1**)

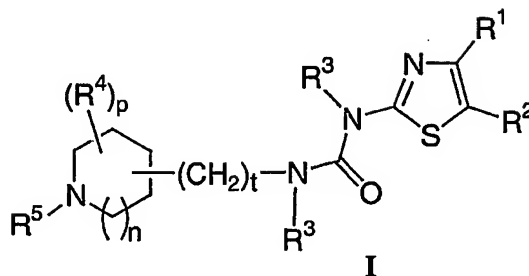
5



Benzyl 4-([[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl] amino)
methyl]piperidine-1-carboxylate **2-2** (125.0mg, 0.3mmol) was placed in to a HF
10 apparatus and charged with HF and anisole. The HF was allowed to evaporate over
night and the residue dissolved into trifluoroacetic acid and the sample purified on a
Waters prep HPLC system to yield 4-([[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl]
amino)methyl] piperidinium trifluoroacetate **5-1**. ¹H-NMR (500 MHz, CDCl₃):
11.00(1H, br s), 7.76 (1H, s), 7.59(2H, br s) 7.56(2H, t, J=7.57), 7.39(2H, t,
15 J=7.81), 7.27(1H, t, J=7.33) 4.24(2H, br d, J=12.70), 2.83(2H, t, J=12.45), 2.75(2H,
t, J=6.95), 1.80(1H, m), 1.73(2H, d, J=13.18), 1.13(3H, d of d). High res. ES MS:
Theoretical Mass 317.1431, Measured Mass 317.1425(C₁₆H₂₀N₄OS+H⁺)

WHAT IS CLAIMED IS:

1. A compound of Formula I



5

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

- n is 0, 1, 2, or 3;
 10 p is 0, 1, or 2;
 t is 0, 1, or 2;

R¹ is H, halo or C₁₋₈ alkyl;

- 15 R² is phenyl, CN, (C=O)NR^aR^b, halo, C₃₋₆ cycloalkyl or -C≡C-R^c;

R³ is independently H, C₁₋₈ alkyl, SO₂R^d, (C=O)R^d, or CO₂R^d;

R⁴ is H, C₁₋₈ alkyl, halo, OH, or C₁₋₈ alkoxy;

20

R⁵ is H, C₁₋₈ alkyl, phenyl, SO₂R^d, (C=O)R^d, or CO₂R^d;

R^a and R^b are independently selected from H, C₁₋₆ alkyl, phenyl, CO₂R^d, (C=O)R^d, and SO₂R^d;

R^c is H, phenyl, or C₁₋₆ alkyl; and

R^d is phenyl, C₁₋₆ alkyl, or benzyl.

5

2. The compound of Claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R² is phenyl or CN.

3. The compound of Claim 2 or a pharmaceutically acceptable salt
10 or stereoisomer thereof, wherein n is 1 or 2.

4. The compound of Claim 3 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹, R³, and R⁴ are H; and R² is phenyl.

15

5. A compound selected from:

benzyl 4-[[[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl] amino)methyl]piperidine-1-carboxylate;

N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea;

N-(5-phenylthiazol-2-yl)-N'-((R,S)-3-aminopiperidin-3-yl)urea; and

20 4-[[[(5-phenyl-1,3-thiazol-2-yl)amino]carbonyl] amino)methyl]piperidine; or a pharmaceutically acceptable salt or stereoisomer thereof.

6. A pharmaceutical composition which is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

25

7. A method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Claim 1.

8. A method of treating cancer or preventing cancer in accordance with Claim 7 wherein the cancer is selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

5 9. A method of treating or preventing cancer in accordance with Claim 7 wherein the cancer is selected from histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma.

10 10. A method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

15 11. A method in accordance with Claim 10 wherein the disease is an ocular disease.

12. A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Claim 1.

20

13. A method of treating or preventing diabetic retinopathy which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Claim 1.

25 14. A method of treating or preventing age-related macular degeneration which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

15. A method of treating or preventing inflammatory diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.
- 5 16. A method according to Claim 15 wherein the inflammatory disease is selected from rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions.
- 10 17. A method of treating or preventing a tyrosine kinase-dependent disease or condition which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 15 18. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.
19. A process for making a pharmaceutical composition which comprises combining a compound of Claim 1 with a pharmaceutically acceptable carrier.
- 20 20. A method of treating or preventing bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets which comprises administering a therapeutically effective amount of a compound of Claim 1.
- 25 21. The composition of Claim 6 further comprising a second compound selected from:
- 1) an estrogen receptor modulator,
 - 2) an androgen receptor modulator,
 - 3) retinoid receptor modulator,
 - 4) a cytotoxic agent,
 - 30 5) an antiproliferative agent,

- 5
- 6) a prenyl-protein transferase inhibitor,
 - 7) an HMG-CoA reductase inhibitor,
 - 8) an HIV protease inhibitor,
 - 9) a reverse transcriptase inhibitor, and
 - 10) another angiogenesis inhibitor.

22. The composition of Claim 21, wherein the second compound is another angiogenesis inhibitor selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-
10 derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-(chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF.

15

23. The composition of Claim 21, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

24. A method of treating cancer which comprises administering a
20 therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

25. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in
25 combination with a compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 30 5) an antiproliferative agent,

- 5
- 6) a prenyl-protein transferase inhibitor,
 - 7) an HMG-CoA reductase inhibitor,
 - 8) an HIV protease inhibitor,
 - 9) a reverse transcriptase inhibitor, and
 - 10) another angiogenesis inhibitor.

26. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy and a compound selected from:

- 10
- 1) an estrogen receptor modulator,
 - 2) an androgen receptor modulator,
 - 3) retinoid receptor modulator,
 - 4) a cytotoxic agent,
 - 5) an antiproliferative agent,
 - 15 6) a prenyl-protein transferase inhibitor,
 - 7) an HMG-CoA reductase inhibitor,
 - 8) an HIV protease inhibitor,
 - 9) a reverse transcriptase inhibitor, and
 - 10) another angiogenesis inhibitor.

20

27. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.

25 28. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a GPIIb/IIIa antagonist.

29. The method of Claim 31 wherein the GPIIb/IIIa antagonist is
30 tirofiban.

30. A method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of Claim 1.

5

31. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.

10

32. A method of treating or preventing preeclampsia which comprises administering a therapeutically effective amount of a compound of Claim 1.

15

33. A method of treating or preventing tissue damage due to bacterial meningitis which comprises administering a therapeutically effective amount of a compound of Claim 1.

34. A method to treat or prevent endometrioses which comprises administering a therapeutically effective amount of a compound of Claim 1.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015717 A3

- (51) International Patent Classification⁷: **A61K 31/33**, 31/42, 31/445, 31/55, C07D 223/16, 417/12 (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number: PCT/US02/27149 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 13 August 2002 (13.08.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/313,374 17 August 2001 (17.08.2001) US (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and (75) Inventors/Applicants (*for US only*): **HARTMAN, George, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **TUCKER, Thomas, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SISKO, John, T.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SMITH, Anthony, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LUMMA, William, C., Jr.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- Published:
— with international search report
- (88) Date of publication of the international search report:
27 November 2003
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 03/015717 A3

(54) Title: TYROSINE KINASE INHIBITORS

(57) Abstract: The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US02/27149

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : 514/183, 212, 326, 371; 540/430, 594; 546/209, 548/192

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183, 212, 326, 371; 540/430, 594; 546/209, 548/192

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS—structure

EAST/WEST—image subclass

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	Database, CAOLUS on STN (Columbus, OH, USA), No.132:334455. '2-Ureidothiazole derivatives, process for their preparation, and their use as antitumor agents' PCT int. appl. (2000), see RN 267431-20-9.	1, 6, 18-19 ----- 2-4,
A	US 6,500,817 B1 (FISCHER et al.) 31 December 2002, see whole article.	1-4, 6, 18-19

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search


25 APRIL 2003

Date of mailing of the international search report

03 JUN 2003

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

 Authorized officer

 CELIA CHANG

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27149

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4, 6, 18-19, n=0

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

IPC-7: A61K 31/33, 31/42, 31/445, 31/55; C07D 223/16, 417/12

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, 6, 18-19 when $n=0$ of formula I, drawn to four membered ring azacyclic compounds.
Group II, claims 1-4, 6, 18-19 when $n=1$ of formula I, drawn to five membered ring azacyclic compounds.
Group III, claims 1-6, 18-19 when $n=2$ of formula I, drawn to six membered ring azacyclic compounds.
Group IV, claims 1-4, 6, 18-19 when $n=3$ of formula I, drawn to seven membered ring azacyclic compounds.
Group V, claims 7-9, drawn to method of treating/prevent cancer.
Group VI, claims 10-11, drawn to method of treating/preventing diseases in which angiogenesis is implicated.
Group VII, claim 12, drawn to method of treating/preventing retinal vascularization.
Group VIII, claim 13, drawn to method of treating/preventing diabetic retinopathy.
Group IX, claim 14, drawn to method of treating/preventing age related muscular degeneration.
Group X, claims 15-16, drawn to method of treating/preventing inflammatory diseases.
Group XI, claim 17, drawn to method of treating/preventing tyrosine kinase-dependent disease.
Group XII, claim 20, drawn to method of treating/preventing bone pathologies.
Group XIII, claims 21-23, drawn to compositions of multiple active ingredients.
Group XIV, claim 24, drawn to method of treating cancer with combination of drug and radiation.
Group XV, claim 25, drawn to method of treating/preventing cancer with multiple drug combination.
Group XVI, claim 26, drawn to method of treating cancer with multiple drug combination and radiation.
Group XVII, claim 27, drawn to method of treating/preventing cancer using formula I and paclitaxel or trastuzumab.
Group XVIII, claims 28-29, drawn to method of treating/preventing cancer using formula I and GPIIb/IIIa antagonist.
Group XIX, claim 30, drawn to method of reducing tissue damage following cerebral ischemia.
Group XX, claim 31, drawn to method of treating/preventing cancer using formula I and COX-2 inhibitor.
Group XXI, claim 32, drawn to method of treating or preventing preeclampsia.
Group XXII, claim 33, drawn to method of treating/preventing tissue damage due to bacterial meningitis.
Group XXIII, claim 34, drawn to method of treating/preventing endometrioses.

The inventions listed as Groups I-XXIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. Under PCT Administrative Instruction Annex B, Part I(f) Markush Practice, paragraph (B)(2)(v),

"When dealing with [Markush] alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be...raised"

In the instant case, at least one Markush alternative of the groups is not novel, see Pevarello et al. CA 132:334455, RN 267431-20-9 which anticipated compounds of formula I when $n=1$.